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Excipients in Livestock Medication

OMRI appreciates the opportunity to comment on excipients for use in medications that are allowed for use in organic production. As we read the current National Organic Program Standards (NOPS)—in particular the prohibition on synthetics used in production at 7 CFR 205.105(a)—there is no provision to allow for the use of synthetic excipients in 205.603. While excipients may be a low priority, they should not be entirely overlooked. Given that excipients may result in adverse environmental impacts or greater persistence of food animal residues of either of the active or the excipients themselves, comprehensive allowance of all excipients may not be compatible with organic principles. In many formulations, the amount of the excipients will exceed the amount of the active ingredient.

The NOSB has recommended a number of medications for use in livestock production, but has not considered the other ingredients in medications. One notable exception to this is the parasiticide ivermectin, where the NOSB recommended that the slow release (SR) bolus be prohibited because of the documented detrimental impact of this formulation on dung beetles and other organisms important for the proper handling of manure in organic farming situations.

We recognize that excipients raise a number of concerns similar to those raised by inert ingredients. However, there are some significant differences. While excipients can also be held as confidential business information, it is OMRI's experience in research TAP reviews that excipients information is more accessible and open than inert ingredients in pesticides. At the same time, OMRI recognizes that there is an error on the National List at 205.603(f)(1) that is in need of technical correction regarding inert ingredients. OMRI suggests that in the course of taking corrective action with respect to inert ingredients used in pesticides allowed for livestock production (as external parasiticides or for livestock facility pests), that the NOSB also address the question of excipients allowed for use in animals drugs.

OMRI originally recommended in 1997 that only those excipients that are Generally Recognized As Safe (GRAS) by the FDA be allowed in organic production. Since the publication of the final rule in 2000, OMRI has had an opportunity to explore the excipients issue more deeply. A number of the TAP reviews have explicitly dealt with excipients, both in considering active substances used in animal production (e.g. parasiticides) and certain food processing ingredients also commonly used in drug delivery (e.g. gelatin and HPMC). After a examining a number of commonly used formulations, it is OMRI's opinion that limiting excipients only to those that are GRAS is

excessive, unnecessary, and counter to the intent of the NOSB in the review of petitioned actives. OMRI believes that the NOSB should recommend a policy that is more inclusive.

FDA has three routes for approval of excipients in new animal drugs:

1.) A determination is made that the substance is "generally recognized as safe" (GRAS) pursuant to Title 21, U.S. Code of Federal Regulations, Parts 182, 184 or 186 (21 CFR 182, 184 & 186);

2.)The substance is approved of a food additive petition as set forth in 21 CFR 171; or

3.) The excipient is referenced in, and part of, an approved new drug application (NDA) for a particular function in that specific drug product.[1]

In addition to GRAS, OMRI believes that those excipients FDA approved for use as food additives also are compatible with organic standards. An excipient that is approved by FDA only as part of a New Drug Application for a specific drug should be considered by the NOSB in context of the TAP review. It may also be possible to consider that excipients used in formulations approved by FDA for over-the-counter use should generally be acceptable, but OMRI found that more review of this is process is needed to make an informed determination.

OMRI offers the following suggestions to allow for the use of synthetic inerts and excipients used in livestock production:

205.603(e) As non-active substances for use with disinfectants, medications, and parasiticides;

(1) As synthetic inert ingredients as classified by the Environmental Protection Agency (EPA), for use with nonsynthetic substances or a synthetic substances listed in this section and used as an active pesticide ingredient in accordance with any limitations on the use of such substances. EPA List 4 - Inerts of Minimal Concern.

(2) As synthetic excipients as classified by the Food and Drug Administration (FDA) for use with nonsynthetic substances or synthetic substances listed in this section and used as an active animal drug in accordance with the limitations on the use of any such substance that:

(i) has been determined by FDA that the substance is "generally recognized as safe" (GRAS) pursuant to Title 21, U.S. Code of Federal Regulations, Parts 182, 184 or 186 (21 CFR 182, 184 & 186);

(ii). is approved as a food additive by a petition set forth in 21 CFR 171; or

[1] International Pharmaceutical Excipients Council of the Americas (trade group website) http://www.ipecamericas.org/

(iii) is reviewed and included with the listed active ingredient in this part

OMRI believes that future TAP reviews of generic livestock medications should include review of common excipients that are not acceptable for use in food and feed. Approval of these drugs by NOSB would then grant approval of the accompanying excipients, or provide limitations on these excipients deemed necessary by the NOSB.

Implementation: The NOSB could recommend that currently approved generic medications be grandfathered to allow excipients in those formulations through the current sunset period (require mandatory review after 5 years.) .At that time, excipients that are not GRAS or permitted food additives would need review as part of the re-considered TAP. This should hold the door open for the five years until sunset during which time the excipients used in a priority list of veterinary prescription drugs and commonly used OTC products could be researched and their compatibility with organic principles determined.

Table 1
Status of Animal Drugs Petitioned to NOSB

Drug	Availability / Restrictions	Notes
Activated Charcoal	OTC	
Aspirin	OTC	Off-label for food animals?
Atropine	Both?	Some aerosol inhalants use chlorofluorocarbons (CFCs)
Bismuth Salicylate	OTC	
Butorphanol	Prescription	
Calcium borogluconate	OTC	
Epinephrine	Both?	Some aerosol inhalants use chlorofluorocarbons (CFCs)
Flunixin	Prescription	
Furosemide	Prescription	
Heparin	OTC?	
Ivermectin	OTC (some may be Prescription?)	Some injectables may be prescription?
Kaolin Pectin	OTC	
Lidocaine	OTC	
Magnesium hydroxide	OTC	
Mineral Oil	OTC	Some may be prescription?
Oxytocin	Prescription	
Procaine	OTC?	Some forms prescription?
Propylene Glycol	OTC	
Xylazine	Prescription	Off-label for food animals

OTC = approved for over the counter sales

Table Two
Examples of Some
Excipients in some Formulated Products

Torbugesic ™
Each ml:
Butorphanol tartrate, USP 10mgCitric acid, USP 3.3 mg
Sodium citrate, USP 6.4mg
Benzethonium chloride, USP 0.1mg
Water for injection, USP q.s.

Anased ™ (other brand name Rompun - *maybe has different excipients!*)
Each ml:
Xylazine hydrochloride equiv. to 100mg of base activity
Methylparaben 0.9mg
propylparaben 0.1mg
sodium citrate dihydrate 5.0mg
water for injection q.s.
pH adjusted with citric acid and sodium citrate

Tolazine ™
Each ml:
tolazoline hydrochloride equivalent to 100 mg base activity
chlorobutanol 5.0mg
tartaric acid 7.8mg
sodium citrate dihydrate 7.8mg
water for injection q.s.
pH adjusted with hydrochloric acid and sodium citrate

Flunixamine ™
Each ml:
flunixin meglumine 50mg
edetate disodium 0.1mg
sodium formaldehyde sulfoxylate 2.5mg
diethanolamine 4.0mg
propylene glycol 207.2mg
phenol (as preservative) 5.0mg
hydrochloric acid
water for injection q.s.

Lidocaine
Each ml:
lidocaine hydrochloride 2.0%
propylene glycol 5.2%
Sodium chloride 0.5%
Sodium lactate 0.5%
Methylparaben 0.15%
Sodium metabisulfite 0.1%
Propylparaben 0.03%
Disodium edetate 0.001%

Epinephrine
Each ml:
epinephrine 1mg
sodium chloride 9mg
chlorobutanol (preservative) 5mg
Sodium m-Bisulfite 1mg
Water for injection q.s.

Heparin
Each ml:
heparin sodium, USP 1000units
sodium chloride 8.6mg
benzyl alcohol 0.01ml in water for injection q.s.
sodium hydroxide and/or hydrochloric acid added, if needed, for pH adjustment. pH5.0-7.5 -

Atropine Sulfate
Each ml:
Atropine sulfate 15mg
Sodium chloride 9mg
Methylparaben 1.8mg
Propylparaben 0.2mg
Water for injection q.s.
pH adjusted with hydrochloric acid and/or sodium hydroxide if necessary

Lasix ™
Each ml:
furosemide 50mg (deferred until this month's meeting)
myristyl-gamma-picolinium chloride 0.02%
EDTA sodium 0.1%
sodium sulfite 0.1%
sodium chloride 0.2%
water for injection q.s.
pH adjusted with sodium hydroxide and/or hydrochloric acid

UAA gel
(300cc tube for oral administration)
Activated hardwood charcoal 100mg/ml
Thermally activated attapulgite clay 200mg/ml
Inert ingredients: water, (gel).

Rumalax bolus
each bolus:
Magnesium oxide 276gr (17.9gm) (equivalent to Magnesium hydroxide, 400gr.) (passed at September meeting)
Flavored with Ginger, Capsicum, and methyl salicylate. Artifical color added.

Oxytocin
Oxytocic activity equivalent to 20USP posterior pituitary units with sodium hydroxide/acetic acid for pH adjustment
Chlorobutanol (as preservative) 2.4mg
Water for injection q.s.

Veta-K1 ™ (Vitamin K)
Each ml:
phytonadione 10mg
Polyoxyehtylated fatty acid derivative 65mg
dextrose monohydrate 37.5mg
butylated hydroxyanisole 1mg
butylated hydroxytoluene 1mg
citric acid 8.4mg
sodium phosphate 43.4mg
Benzyl alcohol 0.9% w/v added as a preservative

Mu-Se ™ (vitamin E with selenium)
Each ml:
sodium selenite 10.95 (equivalent to 5mg selenium)
vitamin E 50mg (as d-alpha tocopherylacetate)
Polysorbate 80 250mg
benzyl alcohol 2% (preservative)
water for injection q.s.
Sodium hydroxide and/or hydrochloric acid may be added to adjust pH

Thanks to Dr. Hubert Karreman, Penn Dutch Cow Care, Bartville PA, for this list of excipients as described in product inserts